
Stabilization of beta-catenin induces pancreas tumor formation.

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Scientific Abstract:

BACKGROUND & AIMS: beta-Catenin signaling within the canonical Wnt pathway is essential for pancreas development. However, the pathway is normally down-regulated in the adult organ. Increased cytoplasmic and nuclear localization of beta-catenin can be detected in nearly all human solid pseudopapillary neoplasms (SPN), a rare tumor with low malignant potential. Conversely, pancreatic ductal adenocarcinoma (PDA) accounts for the majority of pancreatic tumors and is among the leading causes of cancer death. Whereas activating mutations within beta-catenin and other members of the canonical Wnt pathway are rare, recent reports have implicated Wnt signaling in the development and progression of human PDA. Here, we sought to address the role of beta-catenin signaling in pancreas tumorigenesis. **METHODS:** Using Cre/lox technology, we conditionally activated beta-catenin in a subset of murine pancreatic cells in vivo. **RESULTS:** Activation of beta-catenin results in the formation of large pancreatic tumors at a high frequency in adult mice. These tumors resemble human SPN based on morphologic and immunohistochemical comparisons. Interestingly, stabilization of beta-catenin blocks the formation of pancreatic intraepithelial neoplasia (PanIN) in the presence of an activating mutation in Kras that is known to predispose individuals to PDA. Instead, mice in which beta-catenin and Kras are concurrently activated develop distinct ductal neoplasms that do not resemble PanIN lesions. **CONCLUSIONS:** These results demonstrate that activation of beta-catenin is sufficient to induce pancreas tumorigenesis. Moreover, they indicate that the sequence in which oncogenic mutations are acquired has profound consequences on the phenotype of the resulting tumor.

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